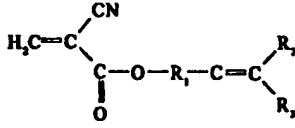




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C09J 4/00, C08F 222/32, A61L 25/00	A1	(11) International Publication Number: WO 99/42535 (43) International Publication Date: 26 August 1999 (26.08.99)
(21) International Application Number: PCT/US99/00991 (22) International Filing Date: 19 January 1999 (19.01.99) (30) Priority Data: 09/025,473 18 February 1998 (18.02.98) US (71) Applicant: CLOSURE MEDICAL CORPORATION [US/US]; 5250 Greens Dairy Road, Raleigh, NC 27616 (US). (72) Inventor: HICKEY, Timothy; 6717 Ebon Court, Raleigh, NC 27615 (US). (74) Agents: OLIFF, James, A. et al.; Oliff & Berridge, PLC, P.O. Box 19928, Alexandria, VA 22320 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: CYANOACRYLATE COMPOSITIONS WITH TERMINAL VINYL GROUP IN THE ALCOHOL PART <div style="text-align: center;">  $\text{H}_2\text{C}=\text{C}(\text{CN})-\text{C}(=\text{O})-\text{O}-\text{R}_1-\text{C}=\text{C}(\text{R}_2)(\text{R}_3) \quad (I)$ </div> (57) Abstract An adhesive composition includes compounds having formula (I) wherein R ₁ is alkyl, alkoxy alkyl, anhydride, ether, ester, or amide, and R ₂ and R ₃ are hydrogen, alkyl, alkoxy alkyl, hydroxy, alkenyl, ester, carboxylic acid or ether and wherein R ₁ is optionally omitted where R ₂ and R ₃ are not both hydrogen.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CYANOACRYLATE COMPOSITIONS WITH TERMINAL VINYL GROUP IN THE ALCOHOL PART

BACKGROUND OF THE INVENTION1. Field of Invention

5 The present invention is directed to monomer compositions useful to form industrial, consumer or medical adhesives and sealants, and methods of applying such compositions. More particularly, this invention relates to monomeric cyanoacrylate compositions having vinyl terminated ester groups that allow a biologically acceptable method of cross-linking through the vinyl group.

10 2. Description of Related Art

U.S. Patent No. 5,624,669 to Leung et al., discloses hemostatic procedures for sealing punctures and incisions in blood vessels and internal organs by applying a cyanoacrylate monomer. Although the cyanoacrylate may polymerize and/or cross-link in vivo, it preferably does so without the need for external sources of physical
15 initiation such as irradiation.

U.S. Patent No. 4,134,929 to Stoakley et al. discloses a polymerizable monomeric allyl 2-cyanoacrylate containing portion comprising an amount of an organic peroxide free radical providing compound sufficient to cause crosslinking of a difunctional monomer diester with the allyl 2-cyanoacrylate. Stoakley discloses that
20 crosslinking may occur by way of the allyl group.

U.S. Patent No. 4,136,138 to Dombroski et al. discloses a polymerizable monomeric 2-cyanoacrylate containing portion comprising an amount of an organic peroxide free radical providing compound sufficient to cause crosslinking of a difunctional monomer diester with the 2-cyanoacrylate. Dombroski discloses that the
25 allyl 2-cyanoacrylate-based adhesive compositions are especially useful as dental adhesives.

U.S. Patent No. 3,975,422 to Buck discloses difunctional monomers where R is an organic linking group derived from a diol or a dihalide of the formula X-R-X, where X is either Cl, Br, I, or hydroxy. The difunctional monomers are employed as
30 crosslinking agents for monofunctional esters of 2-cyanoacrylates. The monofunctional cyanoacrylate monomers may be cyanoacrylates that are terminated by an alkyl, cyclohexyl or phenyl group. Copolymerized compositions of the

monomer blends (difunctional and monofunctional) are useful as adhesives in dental applications. The polymerization of these compositions is initiated by an anionic catalyst or by thermal or other means.

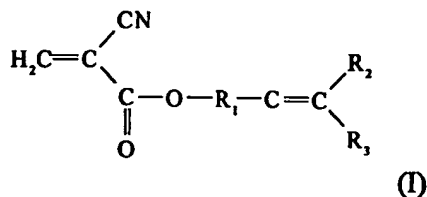
SUMMARY OF THE INVENTION

5 The present invention is directed to monomeric cyanoacrylate compositions having vinyl terminated ester groups that cross-link through the vinyl group, and biomedical uses of such compositions. Cross-linking occurs by way of the vinyl terminated ester groups. In embodiments, chemical durability, flexibility and elasticity of the resulting polymers or copolymers may be increased and degradability
10 can be reduced. In addition, in embodiments high temperatures or ultraviolet initiators may not be needed for cross-linking.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Cyanoacrylate adhesive compositions of the invention contain compounds represented by the following formula (I):

15



wherein R_1 is alkyl, alkoxy, anhydride, ether, ester, or amide, and R_2 and R_3 are independently alkyl, alkoxy, hydrogen, hydroxy, alkenyl, ester, carboxylic acid, ether,
20 or electron withdrawing groups such as halogens, amides, cyanos, esters, acids and ethers. Preferably, R_1 is an alkyl having from about 1 to 8 carbon atoms. Preferably, R_2 and R_3 are hydrogen atoms. More preferably, R_2 and R_3 are alkyl groups having from about 1 to 3 carbon atoms. The R_1 group extends the distance of the R_2 and R_3 groups away from the carbonyl group, thereby making them more chemically
25 accessible and improving chemical durability, flexibility and elasticity of a polymer comprising the monomer. In embodiments, R_1 may be omitted if R_2 and R_3 are not both hydrogen.

In embodiments, the adhesive compositions may additionally contain heat and/or light (e.g., visible or ultraviolet light) activated initiators and accelerators that
30 initiate cross-linking of the cyanoacrylate compounds.

Particular initiators for particular systems may be readily selected by one of ordinary skill in the art without undue experimentation. Suitable polymerization initiators for the cyanoacrylate compositions include, but are not limited to, detergent compositions; surfactants: e.g., nonionic surfactants such as polysorbate 20 (e.g., Tween 20TM), polysorbate 80 (e.g., Tween 80TM) and poloxamers, cationic surfactants such as tetrabutylammonium bromide, anionic surfactants such as benzalkonium chloride or its pure components, stannous octoate (tin (II) 2-ethylhexanoate), and sodium tetradecyl sulfate, and amphoteric or zwitterionic surfactants such as dodecyltrimethyl(3-sulfopropyl)ammonium hydroxide, inner salt; amines, imines and amides, such as imidazole, tryptamine, urea, arginine and povidine; phosphines, phosphites and phosphonium salts, such as triphenylphosphine and triethyl phosphite; alcohols such as ethylene glycol, methyl gallate, ascorbic acid, tannins and tannic acid; inorganic bases and salts, such as sodium bisulfite, magnesium hydroxide, calcium sulfate and sodium silicate; sulfur compounds such as thiourea and polysulfides; polymeric cyclic ethers such as monensin, nonactin, crown ethers, calixarenes and polymeric epoxides; cyclic and acyclic carbonates, such as diethyl carbonate; phase transfer catalysts such as Aliquat 336; and organometallics such as cobalt naphthenate and manganese acetylacetonate and radical initiators.

Suitable initiators for both of the polymerization of the cyanoacrylate and cross-linking of the vinyl group of the composition include, but are not limited to, radicals, such as di-t-butyl peroxide, azobisisobutyronitrile and benzoylperoxide and sodium bisulfite. The polymerizable and/or cross-linkable material may also contain an initiator which is inactive until activated by a catalyst or accelerator (included within the scope of the term "initiator" as used herein). Accelerators for radical initiators such as dimethylaminopyridine and other aminopyridine type molecules may act as an initiator for the cyanoacrylate as well as for the radical polymerization of the vinyl moiety.

In embodiments, when R_1 is omitted and R_2 and/or R_3 are a moiety other than hydrogen, and the composition is to be cationically polymerizable, materials such as strong acids, alkyl iodides (iodomethane), iodine, acetyl perchlorate, and Lewis acids (boron trifluoride, tin tetrachloride, aluminum trichloride, and organometallic derivatives, e.g., $RAICl_2$, R_2AlCl , wherein R is an alkyl group and R_2 is two R groups) may be used.

The monomer compositions of the present invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated internal and/or external tissues; setting fractured bone structures; retarding blood flow from wounds; drug delivery; dressing burns; and aiding repair and regrowth of living tissue.

Conventional surgical adhesive compositions have included plasticizers with the adverse effect of reducing the film strength. It has been discovered that, contrary to prior belief, the film strength (e.g., toughness) under certain conditions is not adversely reduced upon the addition of greater amounts of plasticizing agent. Depending on the particular acidic stabilizing agent and the purity of the monomer utilized in the adhesive composition, the addition of greater amounts of plasticizing agent may increase the toughness of the resulting bond formed on the wound. Acidic stabilizing agents do not significantly affect the polymerization of the monomer in the present composition and provide increased film strength with increasing amounts of plasticizing agents.

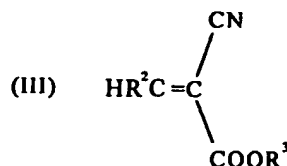
Monomers that may be used in this invention are polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers. In embodiments, the cyanoacrylate composition may comprise a homopolymer of the monomer of formula (I) or a copolymer or terpolymer with other monomers. Such other monomers include, but are not limited to, acrylate monomers, methacrylate monomers, and 1,1-disubstituted ethylene monomers of the formula:



wherein X and Y are each strong electron withdrawing groups, and R is H, $-\text{CH}=\text{CH}_2$, or an alkyl such as methyl, ethyl and other lower alkyls such as butyl and the like, provided that X and Y are both cyano groups, a C_1 - C_4 alkyl group.

Examples of monomers within the scope of formula (II) include alpha-cyanoacrylates, vinylidene cyanides, C_1 - C_4 alkyl homologues of vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $\text{H}_2\text{C}=\text{CX}'\text{Y}'$ wherein X' is $-\text{SO}_2\text{R}'$ or $-\text{SO}_3\text{R}'$ and Y' is $-\text{CN}$, $-\text{COOR}'$, $-\text{COCH}_3$, $-\text{SO}_2\text{R}'$ or $-\text{SO}_3\text{R}'$, and R' is H or hydrocarbyl.

Preferred monomers of formula (II) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula



wherein R^2 is hydrogen or lower alkyl and R^3 is a hydrocarbyl or substituted hydrocarbyl group including polymeric groups; a group having the formula $-\text{R}^4-\text{O}-\text{R}^5-\text{O}-\text{R}^6$, wherein R^4 is a 1,2-alkylene group having 2-4 carbon atoms, R^5 is an alkylene group having 2-4 carbon atoms, and R^6 is an alkyl group having 1-6 carbon atoms; or a group

having the formula
$$\begin{array}{c} -\text{R}^7-\text{C}-\text{O}-\text{R}^8 \\ | \quad | \\ \text{O} \end{array}$$
, wherein R^7 is $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}_2-, -\text{CH}- \end{array}$, or $-\text{C}(\text{CH}_3)_2-$

wherein n is 1-10, preferably 1-5 carbon atoms and R^8 is an organic moiety.

Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1-16 carbon atoms; straight chain or branched chain C_1 - C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

The organic moiety R^8 may be substituted or unsubstituted and may be straight chain, branched or cyclic, saturated, unsaturated or aromatic. Examples of such organic moieties include C_1 - C_8 alkyl moieties, C_2 - C_8 alkenyl moieties, C_2 - C_8 alkynyl moieties, C_3 - C_{12} cycloaliphatic moieties, aryl moieties such as phenyl and substituted phenyl and aralkyl moieties such as benzyl, methylbenzyl and phenylethyl. Other organic moieties include substituted hydrocarbon moieties, such as halo (e.g., chloro-, fluoro- and bromo-substituted hydrocarbons) and oxy- (e.g., alkoxy substituted hydrocarbons) substituted hydrocarbon moieties. Preferred organic moieties are alkyl, alkenyl and alkynyl moieties having from 1 to about 8 carbon atoms, and halo-substituted derivatives thereof. Particularly preferred are alkyl moieties of 4 to 6 carbon atoms.

In the cyanoacrylate monomer of formula (III), R^3 is preferably an alkyl group having 1-10 carbon atoms or a group having the formula $-\text{AOR}^9$, wherein A is a divalent straight or branched chain alkylene or oxyalkylene moiety having 2-8 carbon atoms, and R^9 is a straight or branched alkyl moiety having 1-8 carbon atoms.

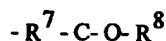
Examples of groups represented by the formula -AOR⁹ include 1-methoxy-2-propyl, 2-butoxy ethyl, isopropoxy ethyl, 2-methoxy ethyl, and 2-ethoxy ethyl.

The preferred alpha-cyanoacrylate monomers used in this invention are 2-octyl cyanoacrylate, dodecyl cyanoacrylate, 2-ethylhexyl cyanoacrylate, butyl cyanoacrylate, methyl cyanoacrylate, 3-methoxybutyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate, or 1-methoxy-2-propyl cyanoacrylate.

The alpha-cyanoacrylates of formula (III) can be prepared according to methods known in the art. Reference is made, for example, to U.S. Patents Nos. 2,721,858 and 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities are preferred for biomedical use.

The alpha-cyanoacrylates of formula (III) wherein R³ is a group having the formula -R⁴-O-R⁵-O-R⁶ can be prepared according to the method disclosed in U.S. Patent No. 4,364,876 to Kimura et al., which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and an alcohol; condensing the cyanoacetate and formaldehyde or para-formaldehyde in the presence of a catalyst at a molar ratio of 0.5-1.5:1, preferably 0.8-1.2:1, to obtain a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

The alpha-cyanoacrylates of formula (III) wherein R³ is a group having the

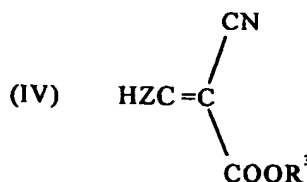


formula $\begin{array}{c} | \\ | \\ O \end{array}$ can be prepared according to the procedure described in U.S.

Patent No. 3,995,641 to Kronenthal et al., which is hereby incorporated by reference herein. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-

cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted
 5 with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic
 10 anhydride.

Examples of monomers of formula (III) include cyanopentadienoates and alpha-cyanoacrylates of the formula:



15 wherein Z is $-\text{CH}=\text{CH}_2$ and R^3 is as defined above. The monomers of formula (IV) wherein R^3 is an alkyl group of 1-10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Patent No. 3,554,990, which is
 20 hereby incorporated by reference herein.

Preferred monomers are alkyl alpha-cyanoacrylates and more preferably octyl alpha-cyanoacrylates, especially 2-octyl alpha-cyanoacrylate. Monomers utilized in the present application should be very pure and contain few impurities (e.g., surgical grade).

25 Compositions of the present invention may include at least one plasticizing agent that imparts flexibility to the polymerized monomer formed on the wound or incision. The plasticizing agent preferably contains little or no moisture and should not significantly affect the polymerization of the monomer.

Other compositions are exemplified by U.S. Patents Nos. 5,259,835 and 5,328,687 and U.S. Patent Applications Serial Nos. 08/609,921, 08/714,288,

08/909,845, 08/755,007, 08/920,876, and 08/488,411, all incorporated by reference herein in their entirety.

Examples of suitable plasticizers include acetyl tributyl citrate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(p-cresyl) phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, trioctyl trimellitate, dioctyl glutarate and mixtures thereof. Preferred plasticizers are tributyl citrate and acetyl tributyl citrate. In embodiments, suitable plasticizers include polymeric plasticizers, such as polyethylene glycol (PEG) esters and capped PEG esters or ethers, polyester glutarates and polyester adipates.

Compositions of the present invention may also include at least one acidic stabilizing agent that inhibits polymerization. Such stabilizing agents may also include mixtures of anionic stabilizing agents and radical stabilizing agents.

Examples of suitable anionic stabilizing agents include, but are not limited to, sultones (e.g., α -chloro- α -hydroxy-*o*-toluenesulfonic acid- γ -sultone), sulfur dioxide, sulfuric acid, sulfonic acid, sulfurous acid, lactone, boron trifluoride, organic acids, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide and mixtures thereof. Preferable anionic stabilizing agents are acidic stabilizing agents of organic acids such as acetic acid or phosphoric acid. In embodiments, the amount of sulfur dioxide stabilizer is less than 100 ppm, preferably 5-75 ppm, and more preferably from about 20-50 ppm. The amount of sultone and/or trifluoroacetic acid is about 500-3000 ppm.

Examples of suitable radical stabilizing agents include hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, p-methoxy phenol, t-butyl catechol, butylated hydroxy anisole, butylated hydroxy toluene, and t-butyl hydroquinone.

Suitable acidic stabilizing agents include those having aqueous pK_a ionization constants ranging from -12 to 7, preferably from about -3.5 to about 6, and more preferably from about 2 to about 5.5. For example, suitable acidic stabilizing agents include: hydrogen sulfide (pK_a 7.0), carbonic acid (pK_a 6.4), triacetylmethane (pK_a 5.9), acetic acid (pK_a 4.8), benzoic acid (pK_a 4.2), 2,4-dinitrophenol (pK_a 4.0), formic acid (pK_a 3.7), nitrous acid (pK_a 3.3), hydrofluoric acid (pK_a 3.2), chloroacetic acid (pK_a 2.9), phosphoric acid (pK_a 2.2), dichloroacetic acid (pK_a 1.3), trichloroacetic acid (pK_a 0.7),

2,4,6-trinitrophenol (picric acid) (pK_a 0.3), trifluoroacetic acid (pK_a 0.2), sulfuric acid (pK_a -3.0), and mixtures thereof.

When adding the above-mentioned acidic stabilizing agents to the adhesive composition, the addition of plasticizing agents in amounts ranging from about 0.5 wt.% to about 16 wt.%, preferably from about 3 wt.% to about 9 wt.%, and more preferably from about 5 wt.% to about 7 wt.% provides increased film strength (e.g., toughness) of the polymerized monomer over polymerized monomers having amounts of plasticizing agents and acidic stabilizing agents outside of the above ranges.

The concentration of the acidic stabilizing agents utilized may vary depending on the strength of the acid. For example, when using acetic acid, a concentration of 80-200 ppm (wt/wt), preferably 90-180 ppm (wt/wt), and more preferably 100-150 ppm (wt/wt) may be utilized. When using a stronger acid such as phosphoric acid, a concentration range of 20-80 ppm (wt/wt), preferably, 30-70 ppm (wt/wt) and more preferably 40-60 ppm (wt/wt) may be utilized. In embodiments, the amount of trifluoroacetic acid is about 100 to 3000 ppm, preferably 500-1500 ppm. In other embodiments, the amount of phosphoric acid is about 10-200 ppm, preferably about 50-150 ppm, and more preferably about 75-125 ppm.

Other compositions are exemplified by U.S. Patents Nos. 5,624,669, 5,582,834, 5,575,997, 5,514,371, 5,514,372, 5,259,835 and 5,328,687, incorporated by reference herein in their entirety. The compositions of the present invention may also include at least one biocompatible agent effective to reduce active formaldehyde concentration levels produced during in vivo biodegradation of the polymer (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites; ammonium sulfite salts; amines; amides; imides; nitriles; carbamates; alcohols; mercaptans; proteins; mixtures of amines, amides, and proteins; active methylene compounds such as cyclic ketones and compounds having a β -dicarbonyl group; and heterocyclic ring compounds free of a carbonyl group and containing an NH group, with the ring made up of nitrogen or carbon atoms, the ring being unsaturated or, when fused to a phenyl group, being unsaturated or saturated, and the NH group being bonded to a carbon or a nitrogen atom, which atom is directly bonded by a double bond to another carbon or nitrogen atom.

Bisulfites and sulfites useful as the formaldehyde scavenger compound in this invention include alkali metal salts such as lithium, sodium and potassium salts, and ammonium salts, for example, sodium bisulfite, potassium bisulfite, lithium bisulfite, ammonium bisulfite, sodium sulfite, potassium sulfite, lithium sulfite, ammonium sulfite, and the like.

Examples of amines useful in this invention include the aliphatic and aromatic amines such as, for example, aniline, benzidine, aminopyrimidine, toluene-diamine, triethylenediamine, diphenylamine, diaminodiphenylamine, hydrazines and hydrazide.

Suitable proteins include collagen, gelatin, casein, soybean protein, vegetable protein, keratin and glue. The preferred protein for use in this invention is casein.

Suitable amides for use in this invention include urea, cyanamide, acrylamide, benzamide, and acetamide. Urea is a preferred amide.

Suitable alcohols include phenols, 1,4-butanediol, d-sorbitol, and polyvinyl alcohol.

Examples of suitable compounds having a β -dicarbonyl group include malonic acid, acetylacetone, ethylacetone, acetate, malonamide, diethylmalonate or another malonic ester.

Preferred cyclic ketones for use in this invention include cyclohexanone or cyclopentanone.

Examples of suitable heterocyclic compounds for use as the formaldehyde scavenger in this invention are disclosed, for example, in U.S. Patent No. 4,127,382 (Perry) which is hereby incorporated by reference herein. Such heterocyclic compounds include, for example, benzimidazole, 5-methyl benzimidazole, 2-methylbenzimidazole, indole, pyrrole, 1,2,4-triazole, indoline, benzotriazole, indoline, and the like.

A preferred formaldehyde scavenger for use in this invention is sodium bisulfite.

In practicing the present invention, the formaldehyde concentration reducing agent, e.g., formaldehyde scavenger compound, is added in an effective amount to the cyanoacrylate. The "effective amount" is that amount sufficient to reduce the amount of formaldehyde generated during subsequent *in vivo* biodegradation of the polymerized cyanoacrylate. This amount will depend on the type of active formaldehyde concentration reducing agent, and can be readily determined without undue experimentation by those skilled in the art.

The formaldehyde concentration reducing agent may be used in this invention in either free form or in microencapsulated form. Other compositions are exemplified by U.S. Patent Application Serial No. 08/714,288, incorporated by reference herein in their entirety.

5 When microencapsulated, the formaldehyde concentration reducing agent is released from the microcapsule continuously over a period of time during the in vivo biodegradation of the cyanoacrylate polymer.

For purposes of this invention, the microencapsulated form of the formaldehyde concentration reducing agent is preferred because this embodiment prevents or
10 substantially reduces polymerization of the cyanoacrylate monomer by the formaldehyde concentration reducing agent, which increases shelf-life and facilitates handling of the monomer composition during use.

Microencapsulation of the formaldehyde scavenger can be achieved by many known microencapsulation techniques. For example, microencapsulation can be carried
15 out by dissolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a formaldehyde scavenger compound in particulate form to the coating polymer/solvent solution under agitation to yield a scavenger concentration of 18% by weight; slowly adding a surfactant-containing mineral oil solution to the polymer solution under rapid agitation; allowing
20 the volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the mineral oil; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The coating polymer for microencapsulating the formaldehyde concentration reducing agent should be polymers which undergo in vivo bioerosion, preferably at rates
25 similar to or greater than the cyanoacrylate polymer formed by the monomer, and should have low inherent moisture content. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

30 Examples of coating materials which can be used to microencapsulate the formaldehyde concentration reducing agent include polyesters, such as polyglycolic acid, polylactic acid, poly-1,4-dioxo-2-one, polyoxalates, polycarbonates, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-b-hydroxybutyrate,

5 copolymers of epsilon-caprolactone and delta-valerolactone, copolymers of epsilon-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters); poly(anhydrides); poly(alkyl-2-cyanoacrylates); poly(dihydropyrans); poly(acetals); poly(phosphazenes);
poly(urethanes); poly(dioxinones); cellulose; and starches.

Examples of the surfactant which can be added to the mineral oil include those commercially available under the designations Triton x-100, Tween 20 and Tween 80.

10 The composition of this invention may further contain one or more adjuvant substances, such as thickening agents, medicaments, or the like, to improve the medical utility of the monomer for particular medical applications.

Suitable thickeners include, for example, polycyanoacrylates, polylactic acid, polyglycolic acid, lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and
15 copolymers of alkyl methacrylates and butadiene. Examples of alkyl methylacrylates and acrylates are poly(2-ethylhexyl methacrylate) and poly(2-ethylhexyl acrylate), also poly(butylmethacrylate) and poly(butylacrylate), also copolymers of various acrylate and methacrylate monomers, such as poly(butyl methacrylate-co-methylacrylate).

To improve the cohesive strength of adhesives formed from the compositions of
20 this invention, difunctional monomeric cross-linking agents may be added to the monomer compositions of this invention. Such crosslinking agents are known. Reference is made, for example, to U.S. Patent No. 3,940,362 to Overhults, which is hereby incorporated by reference herein. Examples of suitable crosslinking agents
include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene
25 dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). A catalytic amount of an amine activated free radical initiator may be added to initiate polymerization of the cyanoacrylate monomer/crosslinking agent blend.

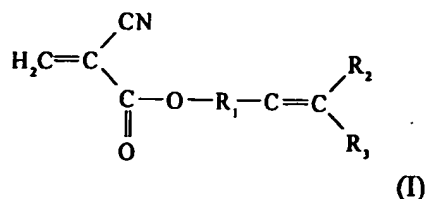
The compositions of this invention may further contain fibrous reinforcement and colorants, i.e., dyes and pigments. Examples of suitable fibrous reinforcement
30 include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenyl-amino]-9,10 anthracenedione (D+C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalene-sulfonic acid (FD+C Yellow No. 6); 9-(o-

carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD+C Red No. 3); 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonic acid disodium salt (FD+C Blue No. 2); and [phthalocyaninato (2-)] copper.

- 5 Depending on the particular requirements of the user, the adhesive compositions of this invention can be applied by known means such as with a swab, glass stirring rod, sterile brush or medicine dropper. However, in many situations a spray dispensing package is preferred in which the adhesive composition is in solution with a compatible anhydrous propellant. Other modes of application are exemplified in U.S. Patent
- 10 Application Serial No. 08/488,411, incorporated by reference herein in its entirety.

WHAT IS CLAIMED IS:

1. An adhesive composition, comprising a compound of the following formula (I):



5

wherein R_1 is selected from the group consisting of alkyl, alkoxy, anhydride, ether, ester, and amide, wherein R_2 and R_3 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, hydroxy, alkenyl, ester, carboxylic acid, ether and electron withdrawing groups, and

10

wherein R_1 is optionally omitted where R_2 and R_3 are not both hydrogen.

2. The adhesive composition according to claim 1, wherein said electron withdrawing groups are selected from the group consisting of halogens, amides, cyanos, esters, acids and ethers.

15

3. The adhesive composition according to claim 1, wherein R_1 is an alkyl having from about 1 to 8 carbon atoms.

4. The adhesive composition according to claim 1, wherein R_2 and R_3 are hydrogen.

20

5. The adhesive composition according to claim 1, wherein R_2 and R_3 are alkyls having from 1 to 3 carbon atoms.

6. The adhesive composition according to claim 1, further comprising an initiator.

7. The adhesive composition according to claim 6, wherein said initiator is selected from the group consisting of benzalkonium chloride, stannous octoate and sodium tetradecyl sulfate.

25

8. The adhesive composition according to claim 1, further comprising a radical initiator.

9. The adhesive composition according to claim 8, wherein said radical initiator is selected from the group consisting of di-t-butyl peroxide, azobisisobutyronitrile and benzoylperoxide.

5 10. A method of joining together surfaces, comprising:
 (a) holding together at least two surfaces to form abutted surfaces,
 and
 (b) applying across said abutted surfaces an adhesive composition according to claim 1.

10 11. An adhesive composition comprising a homopolymer of the compound of claim 1.

 12. An adhesive composition comprising a copolymer of the compound of claim 1 and a 1,1-disubstituted ethylene monomer.

 13. The adhesive composition according to claim 12, wherein said ethylene monomer is n-butyl cyanoacrylate or 2-octyl cyanoacrylate.

15 14. The adhesive composition according to claim 1, wherein crosslinking occurs through the vinyl terminated ester group.

 15. The adhesive composition according to claim 1, further comprising an ultraviolet initiator.

20 16. A manufacture of the adhesive composition of claim 1 for use in a biomedical application selected from the group consisting of drug delivery, burn treatment, setting fractured bone structures, retarding blood flow from wounds, aiding repair and regrowth of living tissue and apposing surgically incised or traumatically lacerated internal or external tissues.

25

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/00991

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C09J4/00 C08F222/32 A61L25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C09J C09D C08F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 527 561 A (ETHICON INC) 4 October 1978 see page 1, line 22 - page 2, line 29 see claims 1-8	1,3,4, 10-12, 14,16
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 75-41560w XP002102219 & JP 49 094742 A (TAOKA DYESTUFF MFG. CO. LTD.), 9 September 1974 see abstract	1,3,4, 11,12,14

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 1999

Date of mailing of the international search report

19/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bettels, B

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 99/00991

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 136 138 A (DOMBROSKI JOHN R ET AL) 23 January 1979 cited in the application see examples see claims	1,3,4,6, 8,12,14, 16
A	WO 97 31598 A (CLOSURE MEDICAL CORP) 4 September 1997 see claims 1,9-11,19,21	1,6,8, 10,12, 13,16
A	US 4 041 062 A (BUCK CARL J) 9 August 1977 see abstract see claims	1,2,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern 1st Application No

PCT/US 99/00991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1527561 A	04-10-1978	US 3995641 A	07-12-1976
		AU 504066 B	04-10-1979
		AU 1325576 A	27-10-1977
		BE 841091 A	25-10-1976
		BR 7602478 A	19-10-1976
		DE 2617525 A	04-11-1976
		FR 2308360 A	19-11-1976
		GB 1527562 A	04-10-1978
		SE 411547 B	14-01-1980
		SE 7604578 A	24-10-1976
		ZA 7602410 A	30-11-1977
US 4136138 A	23-01-1979	NONE	
WO 9731598 A	04-09-1997	AU 1981497 A	16-09-1997
		CA 2247906 A	04-09-1997
		EP 0886507 A	30-12-1998
US 4041062 A	09-08-1977	US 4041063 A	09-08-1977
		US 4041061 A	09-08-1977
		US 4012402 A	15-03-1977